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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/598,696	06/06/2007	Marta Garcia De La Torre	X16661	9065

25885	7590	11/29/2007
ELI LILLY & COMPANY		
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EXAMINER	
O DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
11/29/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary	Application No. 10/598,696	Applicant(s) DE LA TORRE ET AL.	
	Examiner David K. O'Dell	Art Unit 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 September 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 8,9 and 16 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 8, 9, 16 is/are rejected.
- 7) ☒ Claim(s) 8 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>See Continuation Sheet</u> . | 6) <input type="checkbox"/> Other: _____ |

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :27 September 2007 & 8 September 2006.

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DETAILED ACTION

1. Claims 8, 9, 16 are pending in the current application.
2. This application is a 371 of PCT/US05/07051 filed 03/08/2005 which claims priority to U.S. provisional 60/553,184 filed 03/15/2004 and European Application 04380058.0 filed 03/12/2004.

Objections

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "amino-phenoxyethyl-benzamide Opioid Receptor Ligands" or another title that conveys the structure of the compounds.

4. Claim 8 is objected to because of the following informalities: The chemical name "3-(4-[[Methyl-(3-methyl-butyl)-amino]-methyl]-phenoxyethyl)-benzamide", has an open parenthesis with no corresponding closed parenthesis. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 8 9 and 16 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making solvates and hydrates of the claimed compounds.

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The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. “The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims”, *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. In the present case the important factors leading to a conclusion of undue experimentation are the absence of any working example of a formed solvate, the lack of predictability in the art, and the broad scope of the claims.

c) There is no working example of any hydrate or solvate formed. The claims are drawn to solvates, yet the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 “The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist.” The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

g) The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an

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interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). West, Anthony R., "Solid State Chemistry and its Applications, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stable region of the solvate. h) The claims include a presently unknown list of solvents embraced by the term "solvate". Thus, the scope is broad.

The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 103

6. Claims 8, 9 16 are rejected under 35 U.S.C. 103(a) as being obvious over WO 2004/026305 A1 (cited on the IDS) in view of U.S. 6,4105,561. The applied reference has a common assignee and an inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(I)(1) and § 706.02(I)(2). The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determination of the scope and content of the prior art

(MPEP 2141.01)

Blanco-Pilado et. al. teaches two compounds that are analogs of the compounds of the instant case that have the same utility. In particular two compounds on page 32 which is reproduced below:

WO 2004/026305

PCT/US2003/026300

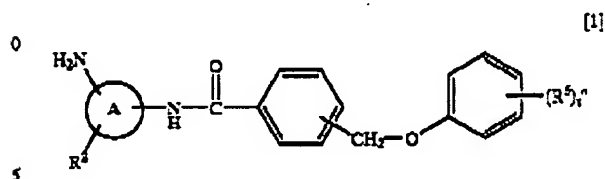
32

4-{{4-[(4-Fluoro-benzylamino)-methyl]-phenoxy}-benzamide,
4-{{4-[(4-Pentylaminomethyl)-phenoxy]-benzamide, ←
4-{{4-[(2-Phenyl-propylamino)-methyl]-phenoxy}-benzamide,
4-{{4-[[2-(2-Chloro-phenyl)-ethylamino]-methyl]-phenoxy}-benzamide,
4-{{4-[[2-(2,4-Dichloro-phenyl)-ethylamino]-methyl]-phenoxy}-benzamide,
4-{{4-[[2-(4-Fluoro-phenyl)-ethylamino]-methyl]-phenoxy}-benzamide, ←
4-{{4-[[2-(3-Fluoro-phenyl)-ethylamino]-methyl]-phenoxy}-benzamide,
4-{{4-[[2-(2-Fluoro-phenyl)-ethylamino]-methyl]-phenoxy}-benzamide,
4-{{4-[[2-(2,5-Dimethoxy-phenyl)-ethylamino]-methyl]-phenoxy}-benzamide,
4-{{4-[[2-(2,6-Dichloro-phenyl)-ethylamino]-methyl]-phenoxy}-benzamide,
4-{{4-[(2-o-Tolyl)-ethylamino]-methyl]-phenoxy}-benzamide,
4-{{4-[(2,2-Diphenyl)-ethylamino]-methyl]-phenoxy}-benzamide,

Shinkai et. al. teach that phenoxymethyl benzamides are pharmacophores associated with opioid receptor activity, see the compounds of columns 7 & 8 and the structure of claim 9.

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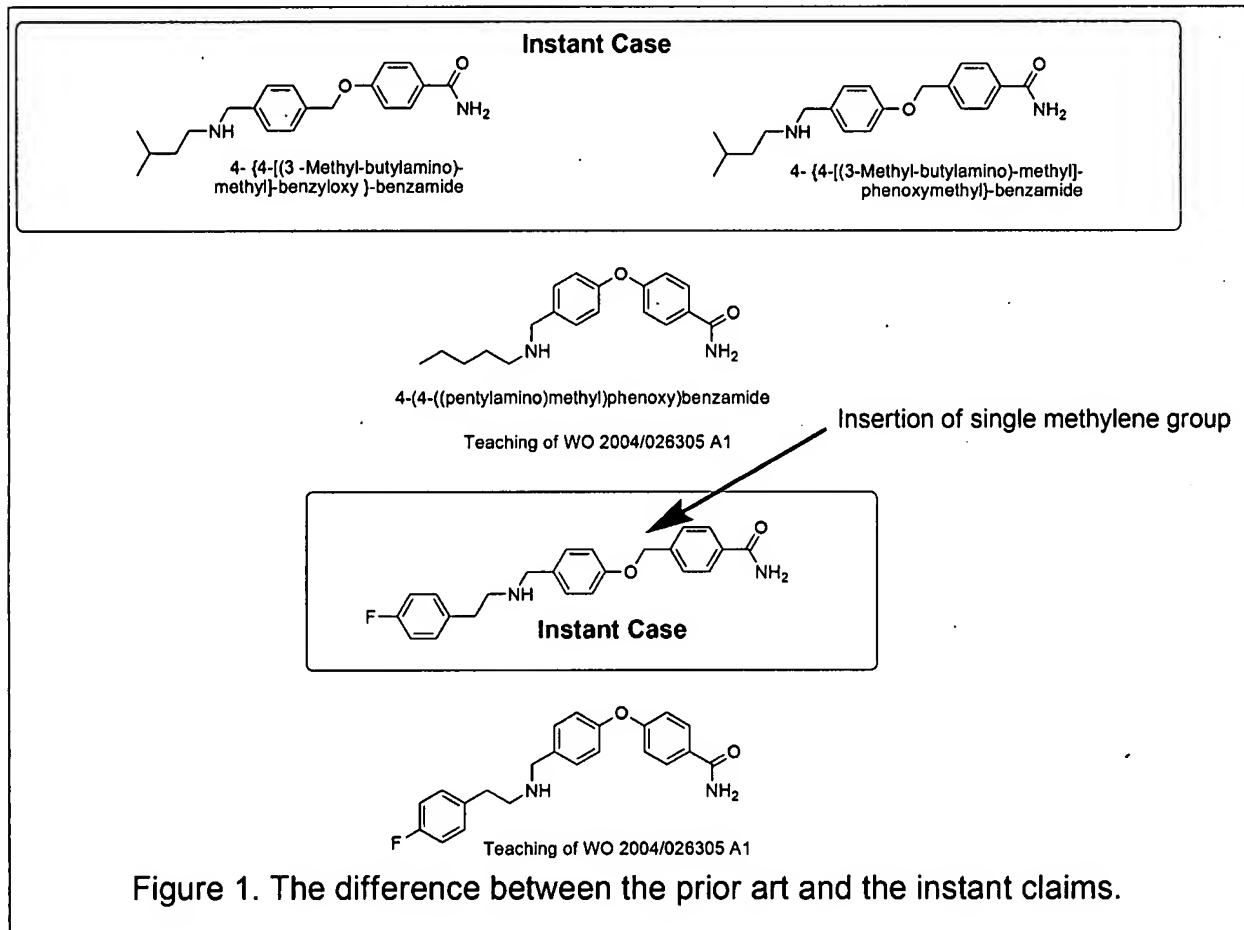
- N-(4-amino-2-methyl-6-quinolyl)-2-[(2-chloro-4-ethylphenoxy)methyl]benzamide hydrochloride,
 N-(4-amino-2-methyl-6-quinolyl)-2-[(4-chloro-3-methylphenoxy)methyl]benzamide hydrochloride,
 N-(4-amino-2-methyl-6-quinolyl)-2-[(2-chloro-4-methylphenoxy)methyl]benzamide hydrochloride,
 N-(4-amino-2-methyl-6-quinolyl)-2-[(4-ethylphenoxy)methyl]benzamide,
 N-(4-amino-2-methyl-6-quinolyl)-2-[(4-chloro-3-methylphenoxy)methyl]benzamide,
 4-[2-[(4-amino-2-methyl-6-quinolyl)carbamoyl]benzyloxy]benzyl acetate hydrochloride,
 N-(4-amino-2-methyl-6-quinolyl)-2-[(4-hydroxymethylphenoxy)methyl]benzamide hydrochloride and
 N-(4-amino-2-methyl-6-quinolyl)-2-[(4-ethylphenoxy)methyl]benzamide hydrochloride monohydrate.
 (9) An amide derivative of the formula [1']



Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Blanco-Pilado et. al. do not expressly teach the compounds of the instant case, however the only difference between these compounds is the presence of a methylene unit separating the phenyl ring from the oxygen. The relationship is illustrated graphically in Figure 1.



Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make analogs of the compounds of Blanco-Pilado et. al to produce the instant invention. This exact modification was known in the art as evidenced by the teaching of Shinkai et. al.. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these compounds on the expectation that such close analogues would have similar properties and upon the routine nature of such experimentation in the art of medicinal chemistry. It would be routine for the chemist to insert a methylene at the point of attachment in order to increase potency and to establish better patent protection for her compounds. See *In re Coes, Jr.* (CCPA 1949) 173 F2d 1012, 81 USPQ 369.

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A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

One of ordinary skill is also one of "ordinary creativity, not an automaton". See *Leapfrog Enterprises Inc. v. Fisher-Price. and Mattel Inc.* UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT "An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at 12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Conclusion

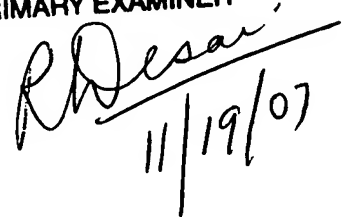
7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

RITA DESAI
PRIMARY EXAMINER
11/19/07